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NERVOUS AND OTHER FORMS OF PROTOPLASMIC TRANSMISSION. I

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IT is an old story that living protoplasm is "irritable." This is one of the many and undeniably important truths of which—as Dr. Johnson used to say—men need to be reminded rather than informed. The whole living cell or tissue, and in many cases the whole organism, *responds* (as we say) to an environmental change by some characteristic change in its own activity. Such inciting changes or *stimuli* may be of the most varied kind; mechanical influences, changes of temperature, light, chemical substances, the electric current may all call forth in an irritable tissue or organism an active response. The precise nature of this response is determined by the special constitution of the living system, and is largely independent of the character of the stimulus; in whatever way it is stimulated a muscle always contracts, a gland secretes, a protozoon carries out a motor reaction. All this is familiar enough. But what is not always clearly recognized, although evident when we stop to consider, is that when a cell, or a whole organism, responds in this way to a single localized stimulus there is always a *transmission* of physiological influence from the point of stimulation to other regions not immediately affected by the stimulating agent. It is because of the ability to transmit such influence that the living system is enabled to react in a unified manner, *i. e.*, as a *whole*. The active state resulting from the local disturbance seems possessed of an innate tendency to spread and to involve the entire cell, and often to extend to other cells. If we reflect we shall see that this is no merely incidental or occasional vital property, specially developed in certain cells or tissues such as nerve, but that any vital response tends to involve a larger area than the area directly receiving the stimulus; that in fact we are dealing here with one of the most general and distinctive peculiarities of living matter. The continued existence of a living cell, and in a larger sense of each living organism, depends upon its acting as a single self-regulating system, the various separate activities of which mutually influence and control one another and are so coordi-

nated as to secure a definite unity of action in the whole. It is by means of such unified and effectively directed action of the *whole* living system upon its environment that its own survival is made possible; and it is plain that any such unification demands prompt and ready transmission of physiological influence from one region to another.

This may be made clearer by a few examples. In animals we usually find that antagonistic pairs of motor processes, which would interfere with each other if they took place at the same time, are so interconnected functionally that their simultaneous occurrence is impossible. Thus flexor and extensor muscle groups can not normally be innervated simultaneously; activity in the one group of controlling motor neurones automatically prevents or decreases activity in the other; *i. e.*, an inhibitory influence is transmitted between the two regions of the central nervous system which innervate the respective muscle-groups. This reciprocal influence is by no means confined to the nervous system. It is shown, for example, in the passage of peristaltic waves along the intestine, in the locomotor movements of worms, and even in amoeboid movement, and apparently forms an essential factor in all motor coordination. Even the more fundamental physiological processes like growth and metabolism are subject to a similar kind of control; in both animals and plants the growth of one part often inhibits the growth of an adjoining part, and it can be shown that the attainment of the normal form and structure in a developing organism depends largely upon such transmitted influences. What is most remarkable is that they control the rate and character of formative and other processes in spatially separate regions of the organism in a manner which often seems independent of any transfer of material substance between the regions concerned; control by material transfer (hormone influence), which is also widespread, is an entirely different type of phenomenon (apparently sometimes confused with the first). Now coordination of activity, functional, metabolic, and formative, is perhaps the most fundamental characteristic of life-processes in general; it is inherent in all vital organization, which, as I need scarcely remind the reader, includes organization of physiological activity as well as of structure. And since this coordination implies that physiological processes in different regions of the cell or organism mutually influence one another, in a constant and dependable manner, it is evident that transmission is a necessary element in any kind of definite response to stimulation. We can not, after the fashion once pre-

vailing in physiology, speak of "irritability" and "conductivity" as if they were two separate and independent properties of protoplasm. Both are always present. When a cell or a nerve-fiber *responds*, it at the same time *conducts*. If it fails to conduct no response is possible. Accordingly we must conclude that the ability to transmit physiological influence from one region to another is common to all forms of living protoplasm. The readiness, completeness and rapidity of this transmission and its precise functional manifestations vary in different cells and in different organisms, but without it normal vital activity is inconceivable. Conduction, in this general physiological sense, is a universal property of living protoplasm.

The problem of the physico-chemical nature of protoplasmic conduction or transmission is thus one of the most fundamental in biology. It includes such problems as that of the nature of the nerve impulse—one often treated in too special and limited a manner by physiologists—and many other special problems of coordination and integration. It is therefore largely a problem for comparative physiology. What kind of influence is it which is thus transmitted? Since living organisms are systems which operate by means of chemical energy freed by oxidation or other chemical changes in cell-constituents, it is obvious that any influence modifying functional activity must first of all be an influence modifying the rate or character of the chemical processes which underlie and determine the function in question. These chemical processes are collectively termed "metabolism." In any form of protoplasmic transmission, therefore, we have an instance of transmission of metabolic influence to a distance; metabolic processes are primarily affected, and along with these the dependent functional activities of the living system. Our general problem accordingly resolves itself into the problem of the means by which chemical or metabolic influence is transmitted from one region of the living system to another more or less distant region. Such transmission is universal in living protoplasm. The main difficulties of the problem arise from the fact that the process may take place independently of the transfer of material between influenced and influencing regions, and often at a very considerable velocity. These peculiarities are well illustrated by the case of nerve-conduction, which may be regarded as the type-phenomenon of the class. What is the essential physico-chemical basis of this type of transmission?

Now that the fundamental problem has been defined, the situation may perhaps be made clearer by a concrete applica-

tion. Most of us are familiar with the behavior of a typical protozoon like *Paramœcium* and will remember what happens when this organism is locally stimulated, for example at its anterior end. A definite sequence of locomotor processes follows, constituting what Jennings has called a "motor reaction." First of all the ciliary stroke is reversed over the whole surface of the body and the animal backs; then the cilia change their direction of stroke in certain regions, causing a turning movement toward the aboral side; and finally the original ciliary stroke is resumed and the animal again swims forward in a different direction. The slight local stimulus sets up some kind of transmitted influence which modifies in a definite and orderly sequence the activity of the motile surface-structures or cilia in different parts of the body. The resulting changes of movement, which unify and coordinate the behavior of the whole organism in a manner which often appears intelligent or consciously adaptive to our eyes, depends upon the transmission of this influence from the original point of stimulation. The transmitted influence follows a definite path, occupies a definite time in its passage, and calls forth a correspondingly definite succession of physiological events. Since the normal physiological sequence is a constant one, we are justified in inferring the existence of some fixed or stable structural and physiological "organization" in the protoplasm, determining the rate, direction and character of the transmitted influence. At least certain definite conduction-paths must be assumed, forming part of the inherited organization and furnishing a ready-formed basis for the constant sequence of motor activities. Transmitted influences of some kind, coordinated both in space and time, evidently control the whole behavior of the animal, and hence determine the possibility of its continued existence as an organic species. And what is true of a single organism like *Paramœcium* is true of countless others and probably of all. There is infinite diversity of detail in different organisms, in correspondence with the diversity in modes of behavior, but in all cases the characteristic sequences of physiological activity and behavior, on which continued normal life depends, are determined by the definite and regulated transmission of physiological influence between different regions of the organism. In higher animals the chief conducting paths are clearly defined anatomically and constitute the central and peripheral nervous system; but even in the individual cells it is probable that equally definite and delicately coordinated pathways of protoplasmic transmission exist, controlling the local differ-

ences of metabolism and functional activity. The case of protozoa shows that there may be such pathways within the limits of single cells.

Many single cells of higher animals exhibit certain simple types of transmission following local injury, which have only recently been studied in detail and deserve particular attention, since they seem to throw light upon the more complex processes of normal protoplasmic conduction. I refer to the transmission of the effects of local mechanical injury in isolated cells like blood-corpuscles and germ-cells, as shown in the recent experimental work of Kite, Chambers and Oliver, using the methods of microdissection.¹ Any cut or puncture of the cell-surface, if sufficiently extensive, or even in some cases a simple contact of the needle, may result in a progressive and often rapid disintegration of the whole cell. Thus a red corpuscle pricked at one point immediately begins to lose hæmoglobin over its entire surface; a leucocyte similarly treated soon disintegrates. Evidently a change in the protoplasmic surface-film, involving loss of semi-permeability, is transmitted from the point of injury over the whole cell. The cell-surface appears to be so constituted that a rapid local alteration of this kind induces automatically a similar change in adjoining areas. Hence the effect *spreads*. There is an essential resemblance between this kind of transmission and the transmission of the excitation-state in irritable elements. In both cases there is evidence of a transmitted alteration in the osmotic properties of the surface-layer;² in the typical irritable element, however, this surface-change is rapidly reversed and the original or "resting" condition is restored, while in the blood-corpuscle the destruction of the surface-layer is permanent and the cell breaks down. It is important to recognize that the transmission of the effects of local alteration is not confined to those specialized cells or cell-structures which we agree to call "irritable"; it is only that in the latter case the transmitted effect is more readily produced, is locally evanescent or reversible, is propagated more rapidly, and calls forth more definite and conspicuous effects than in

¹ Cf. *Science*, 1914, N. S., Vol. 40, pp. 625, 824; Vol. 41, p. 290.

² I. e., a temporary increase of surface-permeability appears to be very generally if not universally associated with stimulation in irritable living cells. This change does not remain localized at the point of stimulation, but spreads rapidly and involves the whole irritable element. It will be seen below that a similar kind of self-propagating surface-change takes place under certain conditions in the surface-film formed at the interface between certain metals and the solutions with which they react (e. g., passive iron in nitric acid, mercury in hydrogen peroxide solution, etc.).

other types of cell. In such cases we are accustomed to regard this property as a special physiological function, and call it "conduction." In nerve it is especially highly developed, and for this and other reasons the transmission of the nerve-impulse has often been regarded as constituting a special problem in itself. Nervous conduction, however, is only one special instance of the more general phenomenon of protoplasmic transmission. Yet because of its many striking characteristics, and also because in this tissue the conduction-process is apparently uncomplicated by other processes, most of the special studies of protoplasmic conduction have been made on nerve. I shall therefore refer largely to the results of such studies in considering, as I shall now attempt to do, the physico-chemical nature of the transmitted influence.

What, then, is the essential nature of this influence? It can not depend upon the bodily transport of material between excited and unexcited areas; its rate is far too rapid for that. In man a stimulating influence is transmitted from the central nervous system to the muscles along the motor nerve-axones (each with a sectional area of perhaps 50 to 100 square microns) at a velocity of 120 meters per second; while the most rapidly diffusing dissolved material particles, the hydrogen ions, move at the rate of only a few centimeters per hour, even under the influence of steep electrical gradients. Nor is the influence mechanical in nature, like (for example) the transmission of signals by the old-fashioned wire bell-pulls, for there is no visible mechanical deformation in a nerve or in a *Paramœcium* during transmission. Change of temperature is also ruled out as a possible factor; in a nerve during the passage of a single nerve-impulse the rise of temperature is estimated by Hill as not more than a hundred millionth of a degree; this fact disposes of the analogy to an explosion-wave, a process which is propagated by local rise of temperature associated with increase of pressure. There is also no resemblance to the transmission of physico-chemical germ-effects, as, *e. g.*, in crystallization; in a tube filled with a supersaturated solution of Na_2SO_4 the introduction of a crystal of the salt at one end causes separation of crystals throughout the whole solution, the effect being propagated rapidly from end to end. But in this case a mechanical and optical change and a rise of temperature accompany the process, and neither of these is perceptible in a conducting nerve. Moreover the crystallization process is not spontaneously reversible, and the rapid reversal of the local change is perhaps the most striking feature of nor-

mal nervous conduction. On reviewing the various known modes of transmission in inorganic processes we find none corresponding even remotely to the protoplasmic process, with the possible exception of some form of electrical influence.

But a comparison with the electric current does not seem at first sight to offer any escape from our difficulties. It is true that we have here a case where rapid transmission of chemical influence to any required distance is possible. We may connect a battery by wires to an electrolytic cell at an indefinite distance; when the circuit is closed chemical processes start simultaneously in both battery and cell; and any change in the rate of the chemical process in either system at once causes corresponding changes in the other. This is a simple consequence of Faraday's law of electrolysis. There are, however, at least two essential differences between chemical transmission of this type and nervous transmission. In the electrical circuit the transmission of chemical influence takes place instantaneously, *i. e.*, at the speed of the electric current (3×10^{10} cm. per second), and the intensity of the chemical effect at the terminals decreases as the length of the conducting path increases, because of the inevitable increase in electrical resistance. Further, in such an arrangement there is always a *circuit*, *i. e.*, two spatially separated metallic paths by which the current respectively leaves and returns to the battery; while in the case of a nerve-axone there is only a single slender fiber of high electrical resistance, which conducts chemical influence with apparently undiminishing intensity along its whole length. This last peculiarity should especially be noted; there is no evidence that the nerve-impulse decreases in its intensity as it passes along the normal nerve; on the contrary there is definite and, I think, conclusive evidence that it maintains its local intensity unaltered.

And yet there are many indications that electrical processes play an essential part in protoplasmic conduction; that in fact the transmission of activity from the excited to the adjoining unexcited areas is directly due to electrical influences. The comparison of the nervous impulse to an electric current through a wire is plainly a false one. Nevertheless, the possibility remains that the transmission is the result of electrical effects of a quite different kind. We know that the activity of a living cell, *e. g.*, a muscle cell, is associated with the production of an electric current, the so-called action-current, and that this current is able to stimulate other muscle-cells. Is it not possible that in a similar manner the electrical disturbance

accompanying activity in one region of a muscle-cell or nerve-fiber may arouse activity in the adjacent still unexcited regions of the same cell or fiber? These regions, on thus secondarily becoming active, would influence similarly the adjoining regions beyond, and in this manner the state of excitation might be transmitted as a wave along the irritable element—each successive region activating the one next beyond by means of the action-current at the boundary between resting and active regions. Such an hypothesis would be free from the objections just cited, and in fact it has been suggested from time to time (although usually in a vague and experimentally unsubstantiated form) by various physiologists from Du Bois-Reymond on.

This general hypothesis, that the bioelectric variation itself constitutes the normal exciting condition in the transmission of local activity from place to place in living cells or nerve-fibers, renders intelligible one of the most remarkable and significant general peculiarities of living organisms, namely, their sensitivity to electrical influences. This sensitivity is so great that in Galvani's early electrical investigations the nerves and muscles of frogs were used as delicate electroscopes in studying the effects of friction and similar treatment upon the electrical condition of bodies.³ And, as all know, the discovery of current-electricity followed from observation of the effects of simultaneous contact of dissimilar metals upon these living tissues. So long as the electric current was regarded as an exclusively artificial or "laboratory" product this highly developed electrical sensitivity of living matter was difficult to understand on teleological or other grounds. It seemed to be a purely incidental peculiarity, probably unconnected with normal function. But we now know that electrical currents are associated with the most various physiological functions, and there is every reason to believe that they are a constant accompaniment of all cell-activities. If this is the case, such currents must constitute a normal feature of the environment of most living cells, at least in multicellular organisms; and that a sensitivity to such currents should exist is no longer surprising. It now seems probable that the bioelectric currents play a general coordinating rôle of the widest possible application in living organisms, and that they form the chief, though not the only, means by which physiological and metabolic influence is transmitted from cell to cell and between different regions of the

³ A striking instance of extreme sensitivity to weak electric currents has recently been discovered by Parker in the catfish. The simple dipping of a metallic rod into the aquarium produces through local action sufficient current to excite the fish. Cf. *Amer. Journ. Physiol.*, 1917, Vol. 44, p. 405.

same cell. Such a view would regard the phenomena of transmission in cells and nerve-fibers as essentially an expression or consequence of electrical effects resulting from local activity. Let us now inquire if the general peculiarities of the bioelectric variations in such a tissue as nerve—which is the best for illustration because it is primarily conducting in function—are in fact consistent with such an hypothesis.

The transmission of the excitation-state in living tissues must have at least this in common with the other innumerable instances of transmission of physical changes in nature—that the change taking place at one region of the transmitting medium or system in some manner produces or determines a similar change at adjoining regions. By a repetition of this effect the state of activity, whatever its special nature may be, is propagated from region to region. Our present problem is: what is the essential physico-chemical nature of the process which takes place at the excited region of a conducting element (like a nerve-fiber) and causes excitation in adjoining resting regions? We have seen that the electrical variation accompanying activity is the only observable change (in nerve at least) which is known to be capable of stimulating a resting part of the same tissue. We are thus led to form the hypothesis that the bioelectric variation at the active region is the direct cause of stimulation at the adjoining resting region. If this can be shown to be the case, transmission is accounted for, since all portions of the tissue are equally sensitive to electrical stimulation. In his Croonian Lecture, delivered in 1912, Keith Lucas formulates the problem with his customary clearness and exactitude. He reviews the various facts indicating that the bioelectric variation is an inseparable feature of the “propagated disturbance,” *i. e.*, of the excitation-wave or nerve-impulse, and proceeds as follows:

Up to the present the available evidence does not contradict the proposition that the electric response is a constant concomitant of the propagated disturbance. But for the purpose of any hypothesis as to the physico-chemical nature of the latter the mere stringent proof of this proposition would not be enough. The important point for any such hypothesis is whether they are identical, *i. e.*, whether the disturbance of electric potential at one point in a nerve is the actual and direct cause of the same phenomenon in a neighboring part. Any hypothesis must be prepared to state whether the electric phenomena play the essential part in propagation or are to be relegated to the position of a mere by-product.⁴

Evidently this distinction is an important one to bear in mind, for it might well be that the electrical variation accompanying

⁴ *Proc. Roy. Soc.*, 1912, Vol. 85, B, p. 507.

the excitation-wave is merely a sign or index of some other underlying process (which determines both the local change and the transmission), and is in itself of no functional importance.

It is necessary first to inquire under what conditions an electric current led into the tissue from outside causes stimulation, and then to inquire whether the current produced by the tissue in its own activity has those characteristics—of intensity, duration, rate of variation, and direction—which will enable it to stimulate the adjoining resting portions of the same tissue. If this is found to be the case, the view that the normal transmission is due to this current will be substantiated; for if the bioelectric current can thus excite the inactive areas, and especially if the rate of this excitation is sufficient to account for the observed velocity of the excitation-wave, there is no reason to seek other causes for the transmission.

In order that an electric current passed through a nerve or other irritable tissue shall cause stimulation, it must have a certain minimal intensity and duration, it must reach that intensity with sufficient rapidity, and it must have a certain direction relatively to the surface of the irritable elements. Too weak a current will not stimulate, nor will one which lasts for too short a time or which rises from zero to its full intensity gradually instead of suddenly. We know, however, from simple observation that in these last respects the current produced by an active muscle or nerve is adequate to stimulate the resting tissue; this is shown by the experiment with the rheoscopic muscle or nerve, in which, *e. g.*, the action current of one muscle is made to stimulate another muscle. The question of the direction of the current relatively to the cell-surface at the region of excitation is more important. In general, electrical stimulation is a *polar* phenomenon; the current stimulates only at the region where the positive stream *leaves* the cell or nerve-fiber; where it enters the cell it causes the reverse effect of inhibition. This is the so-called "law of polar stimulation," which is of very wide if not of universal application in irritable tissues. If the current is led into a nerve by non-polarizable electrodes it can be shown that the excitation-wave arises at the negative electrode or cathode; if the positive electrode is interposed between the cathode and the muscle the excitation-wave may fail to reach the latter because of the inhibitory or "blocking" influence at the anodal region of the nerve. Similar facts apply to muscle; here also where the positive stream leaves the tissue it excites, and where it enters it inhibits. The physiolog-

ical effects produced by breaking the current illustrate the same law, since in this case the reverse polarization-current is to be regarded as the cause of stimulation.

Now when we study the peculiarities of the bioelectric current produced by the conducting tissue in its own activity we are at once struck with the fact that this current has all of those characteristics of intensity, duration, rate of change and direction which would be required if the current were actually *designed* to stimulate the tissue at the adjacent resting regions and bring it again to rest at the active region. All of the conditions required for the automatic transmission of the excitation-state from active to resting regions are in fact present. This may be seen from a consideration of the diagram (Fig. 1).

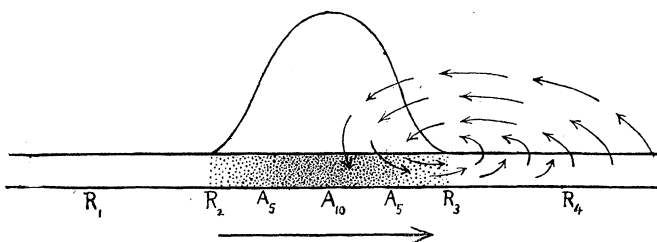


FIG. 1. Diagram of the momentary conditions in a frog's motor nerve at 20° . The shaded region marked A, between R_2 and R_3 , is occupied at the instant under consideration by the excitation-wave, which is regarded as advancing in the direction of the large arrow at the rate of 30 meters per second. Its length, assuming the total duration of the local process (as indicated by the duration of the local bioelectric variation) to be .002 second, is 6 cm. The excitation-process is just beginning at R_3 , has reached its maximum at A_{10} , and has just subsided at R_2 . The curve represents the variation from the resting potential at different points in the active region; the maximum P.D., at A_{10} , is ca. 40 millivolts. The regions marked R are in the resting state. The small arrows indicate the direction of the bioelectric current (positive stream) in a portion of the active-resting circuit. Between R_3 and R_4 its intensity is sufficient to excite the nerve; excitation is thus always being initiated at a distance 3 cm. in advance of the wave-front (*i. e.*, up to R_4). For a somewhat similar distance R_1R_2 in the wake of the excitation-wave the nerve is refractory to stimulation.

The region which is in a state of activity is electrically negative to the regions which are in a state of rest; *i. e.*, there is a circuit in which the positive stream flows in the external medium from inactive to active regions; the current enters the cell-surface at the active region and leaves it at the inactive regions. An external current from a battery having this direction would tend to excite the tissue at R and tend to inhibit an already existing excitation at A (see Fig. 2). There is no apparent reason why a self-generated current should have different physiological effects from one which reaches the tissue from an outside source. Hence we are forced to conclude that the local bioelectric current, as soon as it originates, tends to excite

or activate the resting regions immediately adjoining the active area, and to cut short or inhibit activity in the active area itself. We may compare the active and the adjacent inactive areas with a pair of electrodes applied to the surface of the tissue, with the obvious difference that these areas are continually changing position, keeping pace with the excitation-wave as it advances. The consequence of this is that as each successive

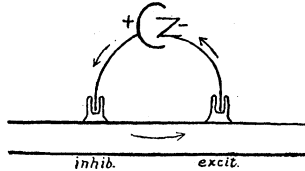


FIG. 2 (inserted for comparison) indicates the effects of passing an external current through a nerve from a battery by non-polarisable electrodes. At the entrance of the current (region corresponding to *A* in Fig. 1) the effect is inhibitory; at its exit (corresponding to *R*) excitatory.

region becomes active, excitation is automatically induced at adjoining regions, and automatically cut short at the active region itself. What we actually observe, quite apart from hypothesis, is that a wave of activity, accompanied by a local electrical circuit, travels in either direction from the original point of excitation. Since this electrical circuit is an essential component of the activation-wave, it is not surprising that the latter produces the characteristic physiological effects of an electric current—excitation at one pole, inhibition at the other—at every region which it traverses in its course. Both the self-propagating and the self-limiting character of the local excitation-process may thus be understood. It should again be noted that excitation at one region, in constant association with simultaneous inhibition at another, is a frequent phenomenon in living organisms, not only in the central nervous system, where it is well-known under Sherrington's term of reciprocal inhibition, but also in locally controlled muscular movements like peristalsis (myenteric law), and even in growth processes and amoeboid movement. The condition observed during the passage of the excitation-wave along a nerve-fiber, where the region *in advance* of the wave-front and that immediately *behind* are oppositely affected, being respectively stimulated and inhibited, is thus in no sense unique or unexampled. A fundamental property of protoplasm, that of being influenced in a polar manner by the electrical current, is apparently the essential factor in all of these phenomena.

Why the excitation-wave continues its progress in the one

direction, and does not strike back, so to speak, may seem to require explanation. Why should not any region of the tissue, when it has once returned to rest, be again excited by the active area which is receding from it, just as it was previously excited by the active area advancing toward it? This effect, however, is rendered impossible by the fact that the tissue always becomes temporarily inexcitable for a brief period (the so-called refractory period) immediately following excitation. The excitation-wave thus leaves behind itself a trail or wake of inexcitable tissue, and by the time any single local region has recovered its normal excitability the region of activity is already at too great a distance in advance to exert any stimulating influence at the recovered region.

It would thus seem that when we take into consideration the fact of an electrical circuit between active and inactive areas, and apply the law of polar stimulation, the wave-like transmission of the active state along the nerve-fiber may be accounted for, if we assume that the intensity of the bioelectric current traversing the resting region at a certain distance in advance of the active region is sufficient for stimulation, and that its duration and time of development at that point meet the chronological requirements of the tissue. It can, however, be shown that this is almost certainly the case. The potential-difference between excited and unexcited areas can be measured, and in a frog's nerve has a value of 30 or 40 millivolts; two platinum electrodes with the same P.D., placed 3 or 4 centimeters part in contact with the nerve, will give a current sufficiently intense for excitation. The normal bioelectric current passing between an active region and an inactive region at a similar distance apart (say 3 cm.) should have the same stimulating efficacy as that between the platinum electrodes, since the P.D. and the conditions of resistance are similar in the two circuits; and there are other facts indicating that the current of the local bioelectric circuit has a sufficient intensity at a distance of two or three centimeters from the active area to stimulate the resting tissue. We know too the duration of the local current and its rate of development; these may be ascertained by measuring the time-relations of the bioelectric variation with the string galvanometer. By this means the local variation of potential at the excited area is shown to occupy a certain time which in a given tissue is definite and characteristic,—*e. g.*, in frog's motor nerve, ca. .002 sec. at 20°, according to Garten's observations;⁵ *i. e.*, the variation rises from zero to its maximum and

⁵ Cf. Garten, Winterstein's "Handbuch der vergleichenden Physiologie," 1910, Vol. 3, Part 2, pp. 135 seq.

subsides at a definite and rapid rate. Lucas and Lapicque have shown for a large variety of tissues from different animals that the normal duration of the bioelectric current and its normal rate of change are closely similar to the duration and rate of change required in the minimal electric current which excites the tissue on being led into it from outside. The tissue is *timed*, as it were, to be excited by a current of a definite duration and rate of change which are essentially the same as those of the current produced by the tissue itself in its own activity. Speaking teleologically, we might say that each tissue is *adapted* to respond to its own action current. It is evident that the rate and degree of the change of potential at the active area will determine the rate of variation and the intensity of the current traversing the unexcited region of the tissue at any fixed distance from that area (see diagram, Fig. 1). The intensity of the portion of current which thus traverses the surface of the nerve-axone at any point will of course depend upon the P.D. and the total electrical resistance of the circuit which includes that point (Ohm's law), and hence will be greater in the immediate neighborhood of the active area than farther away. This implies, however, that there will be a certain minimal distance from the active region at and beyond which the current traversing the resting tissue will be too weak to excite. At all points nearer than this critical distance (R_c in the diagram) there will be excitation. In frog's nerve, as already pointed out, this distance is probably about three centimeters under normal conditions, but it is no doubt subject to considerable variation. The more sensitive the tissue is to weak electric currents the greater this distance will be, and hence the more rapid the rate of transmission. This is probably the chief reason why, in general, highly sensitive tissues conduct rapidly.

We may thus form the following picture of the transmission-process in such a tissue as nerve. At a certain time-interval after the local stimulation the resulting local bioelectric current will cause excitation in the adjoining resting regions of the tissue at all points up to a certain maximal distance beyond the original site of stimulation. These regions on becoming active will at once repeat this effect on regions beyond, and if the excitation-process does not lose in its intensity as it advances along the tissue it is clear that by continued repetition of the same process transmission to any distance is possible. Under such conditions there would be no possibility of the excitation-wave dying out before it reached the end of the tissue, any more than in the case of an ignition-wave in a train of gunpowder. In

both of these instances the energy required for both the local process and the transmission is furnished by the local chemical change; as the wave of chemical activity passes from point to point there is no necessary decrease in the energy available for the local process,—*i. e.*, nothing comparable to the inertia of a moving body, tending to bring the process eventually to a rest. We have, in fact, direct evidence that just such conditions exist in the normal nerve-fiber. The work of Gotch, Lucas and Adrian, and others has shown that in a normal nerve the least stimulus capable of causing excitation produces a response of full intensity; in other words, that the “all-or-none” principle applies to the nerve-fiber as well as to the normal unfatigued voluntary muscle-cell or to cardiac muscle.⁶ Hence at the point R_1 in the diagram, *i. e.*, at the maximal distance in advance of the excitation-wave where the intensity of the local bioelectric current is sufficient for excitation, a full response is elicited; and by continual repetition of this effect the wave travels uninterruptedly along the tissue independently of its distance from the original point of stimulation.

The above account of the conditions of protoplasmic transmission is not so much hypothesis as it is reconstruction of the whole process on the basis of well-established single facts of observation and experiment. But can this conception account for the varying speed at which the excitation-wave travels in different tissues, and especially for the high velocity (120 meters per second) which it attains in the motor nerves of mammals? We can answer this question by considering the rate at which the local excitation-process develops. We have a measure of this rate in the time occupied by the bioelectric variation. It is clear from the diagram that if the local change of potential at any region is quick and prompt the transmission to adjoining regions will be correspondingly rapid, while if it is slow the transmission will also be slow. This is inevitable if the local excitation is directly due to the local current formed between active and inactive regions. A quick rise of this current from zero to its maximum will thus mean quick transmission. And in fact comparative observations show that a close relation exists between the rate at which the local change of potential rises to its maximum and the rate at which the excitation-wave is propagated. In frog's nerve at 18° the upstroke of the action-current curve occupies ca. .001 second; to this corresponds a propagation-velocity of ca. 30 meters per second;

⁶ Cf. Keith Lucas, “Conduction of the Nervous Impulse,” London, 1917, for data and references.

at 32° the corresponding time is approximately halved, ca. .0005 second, and the rate of transmission is doubled. Now if we assume that the current of the bioelectric circuit, as soon as it attains its full intensity, stimulates the resting region at all points up to a distance three centimeters in advance of the region which is already active, we see that at .001 second (at 20°) after excitation has begun at one point it is initiated at a point 3 centimeters in advance of that point.^{6a} This means a transmission-velocity of 30 meters per second. And at a temperature 20° higher, with a temperature-coefficient (Q_{10}) of 2, the rate would be 120 meters per second. Lucas has shown in experiments on the sartorius muscle of the frog that rise of temperature increases the rate of the local variation of potential in almost exactly the same proportion as it increases the rate of transmission.⁷ And in those numerous tissues where the bioelectric variation is slow, the propagation-rate is also slow, as in the non-medullated nerves or the heart-muscle of vertebrates, or the nerves and muscles of many invertebrates. There seems to be no question that the speed of the local variation of potential is the chief factor determining the speed of propagation. It must be understood, however, that other factors play a part and that the proportionality may not be exact, although in the same tissue, as Lucas' work has shown, the parallelism is very close.⁸

Some curious consequences follow from this correlation between the time-relations of the local electric change and the speed of propagation. Since the stimulation of any resting region by the active region adjoining is due to the electric circuit between the two regions, it is essential that the time-factors of excitation should be similar in the two. This is of course normally the case in any single conducting tissue like a nerve, since all regions of the tissue have similar properties. We should expect that the same rule would also apply in the transmission of excitation from one tissue to another, if this kind of transmission is similarly determined; and as a matter of fact comparative observations show that rapidly responding muscles are always innervated by rapidly responding nerves, and vice versa.

^{6a} It must be remembered that the transmission of electric influence from region to region in a circuit is instantaneous (*i. e.*, 3×10^{10} cm./sec.) whether the conductor is metallic or electrolytic.

⁷ K. Lucas, "On the Relation between the Electric Disturbance in Muscle and the Propagation of the Excited State," *Journal of Physiology*, 1909, Vol. 39, p. 207.

⁸ In *Amer. Journ. Physiol.*, 1914, Vol. 34, pp. 417-420, I have given a table showing the relation between the local rate of development of the bioelectric variation and the speed of propagation of the excitation-wave.

Lapicque has shown that there is a general correspondence between the rate of the bioelectric variation in a nerve and that in the muscle which it innervates.⁹ A muscle with a rapid time-factor of excitation—which means a rapid electric variation—contracts rapidly, *i. e.*, has a short single twitch; and a nerve with a rapid time-factor conducts rapidly. Hence quickly contracting muscles are always found to be innervated by quickly conducting nerves,—a relation which Carlson observed years ago,¹⁰ but which has become intelligible only with the development of our modern views of excitation. This relation is simply an incidental consequence of the fact that the electric variation, if it is to stimulate a tissue, must vary at a certain minimal rate which is determined by the nature of the tissue. As Lapicque puts it, the muscle and its innervating nerve are “isochronous,” *i. e.*, have similar time-factors of excitation; if this isochrony is disturbed, as, *e. g.*, in poisoning by curare which slows the excitation-process in muscle, transmission is no longer possible. Accordingly it appears that for transmission from one irritable element to another the time-factors of their respective excitation-processes must coincide, or at least not diverge too widely. Certain other peculiarities of conduction from element to element, such as the irreciprocity of conduction between the neurones in the central nervous system, may perhaps also be explained on the basis of this general principle.¹¹

Another consequence of the present theory of protoplasmic transmission is that under otherwise similar conditions the rate of transmission will be a direct function of the electrical conductivity of the medium. The bioelectric circuit through tissue and medium has naturally a certain ohmic resistance, which is mainly determined (apart from structural conditions) by the nature and concentration of the electrolytes present, since all living tissues are electrolytic conductors. The intensity of the current in the bioelectric circuit at any point (*e. g.*, R_1) a certain distance in advance of the active region will thus be determined by the electrical conductivity of the portion of the circuit which includes that point. Hence a decrease in electrical conductivity should decrease the maximal distance between active and responding regions, *i. e.*, should decrease the rate

⁹ Cf. Lapicque, *Comptes Rendus Soc. Biol.*, 1907, Vol. 13, p. 787, and 1908, Vol. 15, p. 733.

¹⁰ A. J. Carlson, *Amer. Journ. Physiol.*, 1904, Vol. 10, p. 401, and 1906, Vol. 15, p. 136.

¹¹ Cf. my paper cited above, p. 424; also *Science*, N. S., 1918, Vol. 48, p. 58.

of the transmission along the conducting element. In the recent work of Mayer on the propagation-velocity of the nerve-impulse of the medusa *Cassiopea* in sea-water of varying dilutions, a remarkably close parallelism between the electrical conductivity of the medium and the speed of the impulse has in fact been found.¹² If, for example, the electrical conductivity is decreased by a third the rate of transmission is found to be lowered to about the same degree. And in work which Mr. Pond has recently carried out in the Clark laboratory, on the transmission of the contraction-wave in strips of heart-muscle, it was found that dilution of Ringer's solution with isotonic sugar solution causes a definite decrease in the speed of the wave, and that the original speed tends to return if the tissue is replaced in the undiluted salt solution. The relation between electrical conductivity and rate of transmission is not so direct in this case as in Mayer's experiments with *Cassiopea*, but this is hardly to be expected in view of the nature of the tissue and the number of variables involved. It must be remembered that changing the nature of the medium inevitably affects the physiological state of the tissue itself. Mayer finds that it is only if the sea-water is diluted with distilled water, within a certain limited range of dilutions, that electrical conductivity and propagation-velocity vary in a parallel manner. If these limits are exceeded, or if the medium is concentrated instead of diluted, the parallelism fails. If the sea-water is diluted with isotonic $MgCl_2$ solution instead of water, the speed is reduced to about the same degree as if water is used, although electrical conductivity is little changed. In this case the specific depressant influence of magnesium enters as a factor. And change of temperature has a much greater influence on the velocity of propagation than on electrical conductivity. But it is probable that such facts simply obscure without altering the essential dependence of the transmission-rate on electrical conductivity. The latter is only one out of a great variety of factors, some of which are metabolic in nature. If, while keeping temperature constant, we could change the electrical conductivity of the tissue-medium without essentially altering the normal properties of the tissue, the propagation-rate, according to the present theory, should exhibit a close dependence on electrical conductivity. These conditions seem to be approximated in *Cassiopea* when the sea-water is diluted within moderate limits. It is probably because of the remarkable resistance of the *Cassiopea*

¹² A. G. Mayer, *Amer. Journ. Physiol.*, 1917, Vol. 42, p. 469, and 1917, Vol. 44, p. 591.

tissue to injurious influences, including changes in the osmotic pressure of the medium, that the curve of propagation-rate in dilute sea-water follows so closely the curve of electrical conductivity. These results throw an interesting light upon the general physiological significance of the salts always present in living tissues and their surrounding media. Both protoplasm and medium must possess a certain electrical conductivity if the transmission of physiological influence by bioelectric circuits is to be possible. And the inorganic salts of protoplasm may be important largely because they impart this necessary conductivity. We need not assume that this is the only or even the chief rôle of the salts, but it is undoubtedly an essential one.¹³

We have now briefly reviewed the chief characteristics of the conduction-process in living tissues and have come to the conclusion that its physico-chemical basis is essentially a simple one, depending upon the formation of local electrical circuits between the active and the adjoining inactive areas of the tissue. With elements which are sensitive to electrical excitation, and also give rise to electric currents in their own activity, such transmission of excitation is inevitable. If, however, the essential conditions are actually as simple as this, we ought to be able to produce phenomena of the same kind in non-living inorganic systems. There is no apparent reason why this type of transmission-process should be confined to living matter. General evolutionary considerations naturally lead us to this conclusion, since the living has developed from the non-living. We are thus led to inquire if there are in fact any known inorganic processes where transmission of chemical influence takes place under conditions similar to those which we have just described.

(To be concluded)

¹³ The fact that stretching a nerve (within moderate limits, so as not to injure the tissue) leaves its rate of conductivity essentially unaltered is in harmony with the present theory. Evidently some condition which varies directly with *distance, as such*, determines the rate of transmission. This experiment indicates that the interval traversed by the excitation-wave in unit time is not that between two *structurally* defined points of the nerve, but is determined by the length of the column of fluid (*i. e.*, electrolytic solution) between the active and the responding areas (corresponding to the interval between R_3 and R_4 in the diagram). The observed electrical conductivity of any solution is directly proportional to the distance between the electrodes. Cf. Carlson, "Evidence of the Fluidity of the Conducting Substance in Nerve," *Amer. Journ. Physiol.*, 1905, Vol. 13, p. 351, and *ibid.*, 1911, Vol. 27, p. 323; also McClendon, *Proc. Nat. Acad. Sci.*, 1917, Vol. 3, p. 703.